Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1.-25. (Canceled)

26. (Withdrawn) A method for producing a chimeric non-human animal comprising a modified foreign chromosome(s) or a fragment(s) thereof, which comprises the steps of:

(a) preparing a microcell comprising a foreign chromosome(s) or a fragment(s) thereof, and transferring said foreign chromosome(s) or a fragment(s) thereof into a cell with high homologous recombination efficiency through its fusion with said microcell;

(b) in said cell with high homologous recombination efficiency, inserting a vector by homologous recombination into a desired site of said foreign chromosome(s) or a fragment(s) thereof, and/or a desired site of a chromosome(s) derived from said cell with high homologous recombination efficiency, thereby marking said desired site;

(c) in said cell with high homologous recombination efficiency, causing deletion and/or translocation to occur at the marked site of said foreign chromosome(s) or a fragment(s) thereof; and

(d) preparing a microcell comprising said foreign chromosome(s) or a fragment(s) thereof in which deletion or translocation has occurred, and transferring said foreign chromosome(s) or a fragment(s) thereof into a pluripotent non-human animal cell through its fusion with said microcell.

27. (Withdrawn) The method of claim 26, wherein a plurality of said cells with high homologous recombination efficiency are subjected to whole cell fusion after steps (a) and (b) and are subjected to step (c).

28. (Withdrawn) The method of claim 27, wherein a plurality of said cells with high homologous recombination efficiency each comprise a distinct foreign chromosome(s) or a fragment(s) thereof.

29. (Withdrawn) The method of claim 26, wherein said targeting vector comprises a telomere sequence which is introduced into a desired site by insertion of the targeting vector.

30. (Withdrawn) The method of claim 29, wherein said deletion occurs at a site where said telomere sequence has been introduced.

31. (Withdrawn) The method of claim 26, wherein said targeting vector comprises a recognition sequence for a site-directed recombination enzyme, and said recognition sequence is introduced into a desired site by insertion of the targeting vector.

32. (Withdrawn) The method of claim 31, wherein a vector, which is capable of expressing a site-directed recombination enzyme, is introduced into said cell with high homologous recombination efficiency simultaneously with or after insertion of said targeting vector comprising said recognition sequence for a site-directed recombination enzyme, so that an activity of said site-directed recombination enzyme is expressed, resulting in deletion and/or translocation of said foreign chromosome(s) or a fragment(s) thereof at a site into which said recognition sequence is introduced.

33. (Withdrawn) The method of claim 32, wherein said translocation occurs between a plurality of foreign chromosomes or fragments thereof.

34. (Withdrawn) The method of claim 32, wherein said translocation occurs between said foreign chromosome(s) or a fragment(s) thereof and said chromosome(s) derived from said cell with high homologous recombination efficiency.

35. (Withdrawn) The method of claim 31, wherein said site-directed recombination enzyme is a Cre enzyme.

36. (Withdrawn) The method of claim 31, wherein said recognition sequence for site-directed recombination enzyme is a LoxP sequence.

37. (Withdrawn) The method of claim 26, wherein said cell with high homologous recombination efficiency is an embryonic stem cell (or ES cell).

38. (Withdrawn) The method of claim 26, wherein said cell with high homologous recombination efficiency is a chicken DT-40 cell.

39. (Withdrawn) The method of claim 26, which further comprises a step of screening cells comprising a foreign chromosome(s) or a fragment(s) thereof in which deletion and/or translocation has occurred.

40. (Withdrawn) The method of claim 39, wherein said screening is based on expression of a marker gene.

41. (Withdrawn) The method of claim 40, wherein said marker gene is a drug-resistance gene.

42. (Withdrawn) The method of claim 40, the marker gene is a green fluorescent protein-encoding gene derived from the jellyfish Aequorea victoria or a modified gene thereof.

43. (Withdrawn) The method of claim 26, wherein in the step (d), a microcell is produced from said cell with high homologous recombination efficiency; said foreign chromosome(s) or a fragment(s) thereof, in which deletion and/or translocation has occurred is transferred into a CHO cell through its fusion with said microcell; a microcell is produced from the CHO cell; and then said foreign chromosome(s) or a fragment(s) thereof in which deletion and/or translocation has occurred is transferred into a pluripotent cell through its fusion with said microcell.

44. (Withdrawn) The method of claim 26, said pluripotent cell is an embryonic stem cell (or ES cell).

45. (Withdrawn) The method of claim 26, said foreign chromosome(s) or a fragment(s) thereof is derived from a human.

46. (Withdrawn) A method for producing a non-human animal comprising a modified foreign chromosome(s) or a fragment(s) thereof, which comprises the steps of:

(a) preparing a microcell comprising a foreign chromosome(s) or a fragment(s) thereof, and transferring said foreign chromosome(s) or a fragment(s) thereof into a cell with high homologous recombination efficiency thorugh its fusion with said microcell;

(b) in said cell with high homologous recombination efficiency, inserting a vector by homologous recombination into a desired site of said foreign chromosome(s) or a fragment(s) thereof, and/or a desired site of a chromosome(s) derived from said cell with high homologous recombination efficiency, thereby marking said desired site;

(c) in said cell with high homologous recombination efficiency, causing deletion and/or translocation to occur at the marked site of said foreign chromosome(s) or a fragment(s) thereof;

(d) preparing a microcell comprising said foreign chromosome(s) or a fragment(s) thereof, in which deletion and/or translocation has occurred, and transferring said foreign chromosome(s) or a fragment(s) thereof into a cell derived from a non-human animal through its fusion with said microcell; and

(e) transplanting the nucleus of said cell derived from the non-human animal into an enucleated unfertilized egg derived from a homologous non-human animal of the same species.

47. (Withdrawn) The method of claim 46, wherein a plurality of said cells with high homologous recombination efficiency are subjected to whole cell fusion after steps (a) and (b) and are subjected to the step (c).

48. (Withdrawn) The method of claim 47, wherein a plurality of said cells with high homologous recombination efficiency comprise a distinct foreign chromosome(s) or a fragment(s) thereof.

49. (Withdrawn) The method of claim 46, wherein said targeting vector comprises a telomere sequence, which is introduced into a desired site by insertion of the targeting vector.

50. (Withdrawn) The method of claim 49, wherein said deletion occurs at a site into which a telomere sequence has been introduced.

51. (Withdrawn) The method of claim 46, wherein said targeting vector comprises a recognition sequence for site-directed recombination enzyme, and said recognition sequence is introduced into a desired site by insertion of the targeting vector.

52. (Withdrawn) The method of claim 51, wherein a vector, which is capable of expressing a site-directed recombination enzyme, is introduced into said cell with high homologous recombination efficiency simultaneously with or after insertion of said targeting vector comprising said recognition sequence for a site-directed recombination enzyme, so that an activity of said site-directed recombination enzyme is expressed, resulting in deletion and/or a translocation of said foreign chromosome(s) or fragment(s) thereof at a site into which said recognition sequence is introduced.

53. (Withdrawn) The method of claim 52, wherein said translocation occurs between a plularity of foreign chromosomes or fragments thereof.

54. (Withdrawn) The method of claim 52, wherein said translocation occurs between said foreign chromosome(s) or a fragment(s) thereof and said chromosome derived from a cell with high homologous recombination efficiency.

55. (Withdrawn) The method of claim 51, wherein said site-directed recombination enzyme is a Cre enzyme.

56. (Withdrawn) The method of claim 51, wherein said recognition sequence for a site-directed recombination enzyme is a LoxP sequence.

57. (Withdrawn) The method of claim 46, wherein said cell with high homologous recombination efficiency is an embryonic stem cell (or ES cell).

58. (Withdrawn) The method of claim 46, wherein said cell with high homologous recombination efficiency is a chicken DT-40 cell.

59. (Withdrawn) The method of claim 46, which further comprises a step of screening cells containing a foreign chromosome(s) or a fragment(s) thereof in which deletion and/or translocation has occurred.

60. (Withdrawn) The method of claim 59, wherein said screening is based on expression of a marker gene.

61. (Withdrawn) The method of claim 60, wherein said marker gene is a drug-resistant gene.

62. (Withdrawn) The method of claim 60, wherein said marker gene is a green fluorescent protein-encoding gene derived from the jellyfish Aequorea victoria or a modified gene thereof.

63. (Withdrawn) The method of claim 46, wherein, in the step (d), a microcell is produced from said cell with high homologous recombination efficiency; said foreign chromosome(s) or fragment(s) thereof, in which deletion and/or translocation have/has occurred, is/are transferred into a CHO cell through its fusion with the microcell; a microcell is produced from the CHO cell; and then said foreign chromosome(s) or a fragment(s) thereof, in which deletion and/or translocation has occurred, is transferred into a cell derived from a non-human animal through its fusion with the microcell.

64. (Withdrawn) The method of claim 46, said cell derived from a non-human animal is a culture cell derived from an embryo or a blastocyst.

65. (Withdrawn) The method of claim 46, said cell derived from a non-human animal is a culture cell derived from a fetus or an adult.

66. (Withdrawn) The method of claim 46, said cell derived from a non-human animal is a fibroblast cell derived from fetus.

67. (Withdrawn) The method of claim 46, said foreign chromosome(s) or a fragment(s) thereof is derived from a human.

68. (Withdrawn) A non-human animal, which retains a chromosomal fragment(s) obtained by deletion of a foreign chromosome(s) or a fragment(s) thereof.

69. (Withdrawn) The non-human animal of claim 68, wherein said chromosomal fragment(s) comprises:

(i) a marker gene and a telomere sequence, and/or

(ii) a recognition sequence for a site-directed recombination enzyme.

70. (Withdrawn) A non-human animal, comprising a recombinant foreign chromosome(s) obtained by translocation between a plurality of foreign chromosomes or fragments thereof.

71. (Withdrawn) The non-human animal of claim 70, wherein said recombinant chromosomal fragment(s) comprises:

(i) a marker gene and a telomere sequence; and/or

(ii) a recognition sequence for a site-directed recombination enzyme.

72. (Withdrawn) The non-human animal of claim 70, wherein said recombinant foreign chromosome(s) is independently maintained in the nucleus of the non-human animal cell.

73. (Withdrawn) The non-human animal of claim 70, wherein said recombinant foreign chromosome(s) is derived from a human.

74. (Withdrawn) The non-human animal of claim 70, wherein the recombinant foreign chromosome(s) is derived from human chromosomes #14 and #2.

75. (Withdrawn) The non-human animal of claim 70, wherein said recombinant foreign chromosome(s) is derived from human chromosomes #14 and #22

76. (Withdrawn) The non-human animal of claim 70, wherein said recombinant foreign chromosome(s) comprises genes for a heavy-chain and a light-chain of a human antibody.

77. (Withdrawn) The non-human animal of claim 70, wherein said recombinant foreign chromosome(s) comprises genes for a heavy-chain and a light-chain * gene of a human antibody.

78. (Withdrawn) The non-human animal of claim 70, which is a mouse.

79. (Withdrawn) The non-human animal of claim 70, which is an ungulata.

80. (Withdrawn) The non-human animal of claim 70, which is a bovine.

81. (Withdrawn) The non-human animal of claim 70, which is an ovine.

82. (Withdrawn) The non-human animal of claim 70, which is an avian.

83. (Withdrawn) The non-human animal of claim 70, which is a chicken.

84. (Canceled)

85. (Withdrawn) A method for modifying a foreign chromosome(s) or a fragment(s) thereof in a cell, which comprises the steps of:

(a) preparing a microcell containing a foreign chromosome(s) or a fragment(s) thereof, and transferring said foreign chromosome(s) or a fragment(s) thereof into a cell with high homologous recombination efficiency through its fusion with the microcell;

(b) in said cell with high homologous recombination efficiency, inserting a targeting vector by homologous recombination into a desired site of said foreign chromosome(s) or a fragment(s) thereof and/or a desired site of a chromosome(s) derived from said cell with high homologous recombination efficiency, thereby marking said desired site; and

(c) in said cell with high homologous recombination efficiency, causing deletion or translocation to occur at the marked site of said foreign chromosome(s) or a fragment(s) thereof.

86.-92. (Canceled)

93. (Currently amended) A recombinant chromosome comprising:

(i) the centromere of human chromosome #14;

(ii) two telomere sequences;

(iii) at least one recognition sequence for a site-directed recombination enzyme;

(iv) at least two chromosome fragments that had not been adjacently located in a natural chromosome or in a naturally occurring chromosome fragment; and

(v) ~~(iv)~~ a marker gene,

wherein said recognition sequence for a site-directed recombination enzyme is located between said two chromosome fragments.

94. (Previously presented) The recombinant chromosome of claim 93, wherein (A) said centromere is contained within a human chromosome #14 fragment and (B) said

recombinant chromosome comprises at least one chromosome fragment that is not naturally located adjacent to said human chromosome #14 fragment.

95. (Previously presented) The recombinant chromosome of claim 94, wherein said human chromosome #14 fragment is a centromere-comprising portion of the chromosome fragment denoted as SC20.

96. (Previously presented) The recombinant chromosome of claim 93, wherein one chromosome fragment is a fragment of human chromosome #2.

97. (Previously presented) The recombinant chromosome of claim 93, wherein one chromosome fragment is a fragment of human chromosome #22.

98. (Currently amended) The recombinant chromosome of claim 93, **wherein one of the chromosome fragments is** ~~comprising~~ a human chromosome #14 fragment and **wherein another one of the chromosome fragments is** a human chromosome #2 fragment.

99. (Previously presented) The recombinant chromosome of claim 98, wherein said chromosome #14 fragment comprises a human antibody heavy-chain gene locus and said chromosome #2 fragment comprises a human antibody light-chain kappa gene locus.

100. (Previously presented) The recombinant chromosome of claim 98, wherein said chromosome #14 fragment comprises the entire region of the human antibody heavy-chain gene locus and said chromosome #2 fragment comprises the entire region of the human antibody light-chain kappa gene locus.

101. (Currently amended) The recombinant chromosome of claim 93, **wherein one of the chromosome fragments is** ~~comprising~~ a human chromosome #14 fragment and **wherein another one of the chromosome fragments is** a human chromosome #22 fragment.

102. (Previously presented) The recombinant chromosome of claim 101, wherein said chromosome #14 fragment comprises a human antibody heavy-chain gene locus and said chromosome #22 fragment comprises a human antibody light-chain lambda gene locus.

103. (Previously presented) The recombinant chromosome of claim 101, wherein said chromosome #14 fragment comprises the entire region of the human antibody heavy-chain gene locus and said chromosome #22 fragment comprises the entire region of the human antibody light-chain lambda gene locus.

104. (Previously presented) The recombinant chromosome of claim 93, which is generated by chromosome recombination between the chromosome fragment denoted as SC20 and another chromosome fragment.

105. (Previously presented) The recombinant chromosome of claim 104, wherein said recombinant chromosome comprises the entire region of the human antibody heavy chain gene locus.

106. (Previously presented) The recombinant chromosome of claim 104, which is generated by chromosome recombination between the chromosome fragment denoted as SC20 and a fragment of a chromosome other than the human chromosome #14.

107. (Previously presented) The recombinant chromosome of claim 106, wherein the fragment of a chromosome other than the human chromosome #14 is a fragment of a human chromosome #2, which comprises a human antibody light-chain kappa gene locus.

108. (Previously presented) The recombinant chromosome of claim 106, wherein the fragment of a chromosome other than the human chromosome #14 is a fragment of human chromosome #22, which comprises a human antibody light-chain lambda gene locus.

109. (Previously presented) The recombinant chromosome of claim 93, which comprises both a human antibody heavy-chain gene locus and a human antibody light-chain gene locus.

110. (Previously presented) The recombinant chromosome of claim 93, which comprises both the entire region of the human antibody heavy-chain gene locus and the entire region of the human antibody light-chain gene locus.

111. (Previously presented) The recombinant chromosome of claim 93, wherein said recognition sequence is the loxP sequence and said site-directed recombination enzyme is the Cre recombinase.

112. (Previously presented) The recombinant chromosome of claim 93, wherein said recognition sequence is the FRP sequence and said site-directed recombination enzyme is the FLP recombinase.

113. (Currently amended) A recombinant chromosome, which comprises:

(i) the centromere sequence of a human chromosome #21;

(ii) two telomere sequences;

(iii) at least one recognition sequence for site-directed recombination enzyme;

(iv) at least two chromosome fragments that had not been adjacently located in a natural chromosome or in a naturally occurring chromosome fragment; and

(v) ~~(iv)~~ a marker gene,

wherein said recognition sequence for a site-directed recombination enzyme is located between said two chromosome fragments.

114. (Previously presented) The recombinant chromosome of claim 113, wherein (A) said centromere is contained within a human chromosome #21 fragment and (B) said recombinant chromosome comprises at least one chromosome fragment that is not naturally located adjacent to said human chromosome #21 fragment.

115. (Previously presented) The recombinant chromosome of claim 113, wherein said recognition sequence is the loxP sequence and said site-directed recombination enzyme is the Cre recombinase.

116. (Previously presented) The recombinant chromosome of claim 113, wherein said recognition sequence is the FRP sequence and said site-directed recombination enzyme is the FLP recombinase.

117. (Previously presented) A method for producing a recombinant chromosome, comprising:

(a) preparing a first isolated cell comprising a fragment of human chromosome #14 that has a centromere and a recognition sequence for a site-directed recombination enzyme positioned at desired site in said fragment;

(b) preparing a second isolated cell comprising a second chromosome fragment, which comprises a recognition sequence for a site-directed recombination enzyme positioned at desired site in said second chromosome fragment;

(c) fusing said first cell with said second cell to produce a hybrid cell; and

(d) expressing a site-directed recombination enzyme in said hybrid cell,

wherein said enzyme causes site-directed recombination between said fragment of human chromosome #14 and said second chromosome fragment to generate a recombinant chromosome, wherein said recombinant chromosome comprises the centromere of human chromosome #14 and a portion of the second chromosome fragment.

118. (Previously presented) The method of claim 117, wherein said recombinant chromosome is transferred from said hybrid cell into a new cell type via microcell fusion.

119. (Previously presented) The method of claim 118, wherein said new cell type is a CHO cell.

120. (Previously presented) The method of claim 117, wherein said first cell and said second cell are chicken DT-40 cells.

121. (Previously presented) The method of claim 117, wherein said site-directed recombination is detected by the expression of a reporter gene.

122. (Previously presented) The method of claim 121, wherein said reporter gene is a green fluorescent protein gene or functional variant thereof.

123. (Previously presented) The method of claim 117, wherein said recognition sequence in said human chromosome #14 fragment and said recognition sequence in said second chromosome fragment are loxP sequences, and said site-directed recombination enzyme is the Cre recombinase.

124. (Previously presented) The method of claim 117, wherein said recognition sequence in said human chromosome #14 fragment and said recognition sequence in said second chromosome fragment is the FRP sequence and said site-directed recombination enzyme is the FLP recombinase.

125. (Previously presented) The method of claim 117, said human chromosome #14 fragment is the chromosome fragment denoted as SC20.

126. (Previously presented) The method of claim 117, said second chromosome fragment is a fragment of either human chromosome #2 or human chromosome #22, comprising a human antibody light chain gene locus.

127. (Previously presented) A method for producing a recombinant chromosome, comprising:

(a) preparing a first isolated cell comprising a fragment of human chromosome #21 that has a centromere and a recognition sequence for a site-directed recombination enzyme positioned at desired site in said fragment;

(b) preparing a second isolated cell comprising a second chromosome fragment, which comprises a recognition sequence for a site-directed recombination enzyme positioned at desired site in said second chromosome fragment;

(c) fusing said first cell with said second cell to produce a hybrid cell; and

(d) expressing a site-directed recombination enzyme in said hybrid cell,

wherein said enzyme causes site-directed recombination between said fragment of human chromosome #21 and said second chromosome fragment to generate a recombinant chromosome, wherein said recombinant chromosome comprises the centromere of human chromosome #21 and a portion of the second chromosome fragment.

128. (Previously presented) The method of claim 127, wherein said recombinant chromosome is transferred from said hybrid cell into a new cell type via microcell fusion.

129. (Previously presented) The method of claim 128, wherein said second cell is a CHO cell.

130. (Previously presented) The method of claim 127, wherein said first cell and said second cell are chicken DT-40 cells.

131. (Previously presented) The method of claim 127, wherein said site-directed recombination is detected by the expression of a reporter gene.

132. (Previously presented) The method of claim 131, wherein said reporter gene is a green fluorescent protein gene or functional variant thereof.

133. (Previously presented) The method of claim 127, wherein said recognition sequence in said human chromosome #21 fragment and said recognition sequence in said second chromosome fragment are loxP sequences, and said site-directed recombination enzyme is the Cre recombinase.

134. (Previously presented) The method of claim 127, wherein said recognition sequence in said human chromosome #21 fragment and said recognition sequence in said second chromosome fragment is the FRP sequence and said site-directed recombination enzyme is the FLP recombinase.

135. (Previously presented) A cell comprising the recombinant chromosome of any one of claims 93 or 113.

136. (Previously presented) The method of claim 117, wherein said recognition sequence for a site-directed recombination enzyme is positioned at said desired site in said human chromosome #14 fragment and said second chromosome fragment by a targeting vector.

137. (Previously presented) The method of claim 127, wherein said recognition sequence for a site-directed recombination enzyme is positioned at said desired site in said human chromosome #21 fragment and said second chromosome fragment by a targeting vector.

138. (Previously presented) The method of claim 122, wherein said green fluorescent protein gene or functional variant thereof, is obtained from the jellyfish *Aequorea victoria.*

139. (Previously presented) The method of claim 132, wherein said green fluorescent protein gene or functional variant thereof, is obtained from the jellyfish *Aequorea victoria.*

140. (Previously presented) A chromosome vector comprising: (i) a chromosome fragment comprising the centromere of human chromosome #21; (ii) two telomere sequences; (iii) at least one recognition sequence for a site-directed recombination enzyme; and (iv) a marker gene.

141. (Previously presented) The chromosome vector of claim 140, wherein said chromosome fragment is a fragment of human chromosome #21.

142. (Previously presented) The chromosome vector of claim 140, wherein said recognition sequence is the loxP sequence and said site-directed recombination enzyme is the Cre recombinase.

143. (Previously presented) The chromosome vector of claim 140, wherein said recognition sequence is the FRP sequence and said site-directed recombination enzyme is the FLP recombinase.